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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,665	10/18/2004	Elena Cattaneo	CATTANEO ET AL 1 PCT	4253

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WILLIAM COLLARD
COLLARD & ROE, P.C.
1077 NORTHERN BOULEVARD
ROSLYN, NY 11576

EXAMINER	
LEAVITT, MARIA GOMEZ	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/511,665	CATTANEO ET AL.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04-04-2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group I (claims 1-16) in the reply filed on 09-29-2006 is acknowledged.

With regard to restriction requirements, Applicant election of species is acknowledged for the following species: chloramphenicol acetyle transferase as a reporter gene, which reads on claim 3, and neuronal cells which reads on claims 8 and 9.

Claims 17-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected invention, there being no allowable generic or linking claim.

Response to arguments

Applicant's arguments in view of the official restriction/election requirements of 07/31/06 have been respectfully reconsidered. In response to applicant's assertion that inventions of Groups I-III are directed to a unitary inventive concept, namely, a method for preventing and treating Huntington's disease with an NRSE inhibitor and as such a simultaneous search for the Groups I-III together does not constitute an unreasonable search for the examiner, the argument has not been found persuasive as Applicant's traversal has not adequately addressed the examiner's bases for rejection

As stated in the previous office action mailed on 07/31/06, inventions of Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features.

Prior art has described inhibitors of the NRSE such as the repressor protein, neuron-restrictive silencer factor (NRSF) (Kuwahara et al., Molecular and Cellular Biology, March 2001, p. 2085-2097, Vol. 21, No. 6, Abstract). Therefore, the technical feature linking the invention of groups I, II and III does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over prior art for the reasons set forth above.

Therefore claims 1-16 are currently pending for examination to which the following grounds of rejection apply.

Claim objection

Claim 1 objected to because of the following informalities: abbreviations such as NRSE should be spelled out at the first encounter in the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112- second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and dependent claims 2-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. While all of the technical details of a method need not to be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practice. The only disclosed step in claim 1 is the ability of a molecule to inhibit the activity of the NRSE element is evaluated. The omitted steps, for example, can be: incubating said molecule with a cellular system stably transfected with the Neuron Restrictive Silencer Element (NRSE) sequence inserted upstream of a reporter gene, and evaluating of inhibition of the NRSE sequence activity by measurement of gene reporter activity. Even if the evaluating language is used (claim 16 also recites such language), it is not apparent as to under what structural or functional parameters the evaluation is indicative or correlative to the preamble of the claims.

Claims 1 and dependent claims 2-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the NRSE". What is "the NSRE" since there are multiple NRSE-like sequences; therefore, there is insufficient antecedent basis for this limitation in the claim. See, genes containing NRSEs elements with alignment of conserved homologous sequences disclosed in Anderson et al., US. Patent 5,935,811 (Date of publication Aug. 10, 1999; col. 2 lines 45-65 and Figures 1A and 1B).

Claim Rejections - 35 USC § 112 - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for claims directed to:

a method for the selection of molecules active in the prevention and/or treatment of Huntington's Disease wherein the ability of said molecules to inhibit the activity of the NRSE element is evaluated;

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claim

The claims, when given the broadest possible interpretation, encompass a method for selection of molecules able to prevent and/or treat Huntington's disease resulting from the evaluation of said molecule to inhibit the activity of NRSE.

The specification teaches the identification of the cortical brain-derived neurotrophic factor (BDNF) gene promoter and specific DNA element on which wild type huntingtin exerts its action (p. 16). Additionally, the specification discloses the mechanism by which wild-type huntingtin (HD) influences BDNF production in normal brains by maintaining the repressor element transcription factor (REST) in the cytoplasm and reducing levels of REST in the nucleus. Moreover, the specification contemplates a method for *in vitro* testing of molecules by assessing their ability to inhibit the activity of the NRSE element and thus increase BDNF transcription.

The specification provides insufficient data to enable claims directed to the method as broadly claimed. Thereby, specific issues including the correlation between increased expression of BDNF by a test molecule inhibiting the activity of NRSE and treatment and/prevention of Huntington's Disease and identification of mechanisms by which a test molecule inhibiting the activity of NRSE protect from neuronal cell death

in Huntington's Disease patients have to be examined and considered for patentability regarding the broadly claimed methods.

Guidance in the Specification and working example

The instant specification discloses that wild-type huntingtin up-regulates transcription of BDNF (p. 16 and Tables 1 and 2). Moreover, the specification disclose the construction of three BDNF promoters-reporter genes vectors (i.e. BDNF II 1.1 CAT, BDNF II 0.3 CAT, and BDNF II 0.3 MUT CAT) comprising CAT as a reporter gene for transfection experiments in cell culture of CNS overexpressing full-length wild type HD or mutant HD. Results teach that secreted BDNF was significantly higher for cells overexpressing full-length wild type HD in relation to parental cell and was significantly lower for cell expressing mutant HD (p. 17-19). These results indicate a connection between wild type HD and stimulation of BDNF secretion.

The specification is silent about any *in vivo* data teaching a correlation between wild-huntingtin upregulation of BDNF production in the striatum and treatment and/or prevention of Huntington's Disease. The detail of the disclosure provided by the Applicant, in view of the prior Art, must encompass a wide area of knowledge to enable one of ordinary skill in the art at the time of the invention to practice the invention without undue experimentation. However, as it will be discussed below this undue experimentation has not been overcame by the as-filed application. Though the specification teaches an *in vitro* assay for identification of molecules that inhibit the activity of the NRSE element, the broad aspects of treating or preventing Huntington's disease is not reasonably enable for the full scope embraced by the claims.

State of the prior art

Though prior art teaches that wild-type huntingtin activity is important for maintenance of the striatal neurons that selectively die in Huntington's Disease and these neurons require BDNF for their survival and differentiation (Zuccato et al., Nature, 2001, p. 493-498; p. 493, col.2), prior art indicates that the events involved in degeneration of cell neurons death, specially in the striatum, causing hyperactivation of the motor cortex resulting in involuntary movement in Huntington's disease may be more complicated (Cattaneo et al., Scientific American, 2002, pp. 61-65). Huntington's disease is an inherit disorder wherein generation of a mutated form of HD shut off excitatory signals from the motor cortex affecting movement. The state of the prior art is exemplified by Cattaneo, which suggests and teaches that there is not yet a direct correlation between an increased activity of BDNF and an efficacy in treating HD, let alone a prevention of HD (e.g., Cattaneo et al., p. 61, paragraph 2). While it is apparent from the prior art of record that HD in some patients causes a reduction of BDNF expression, the complex pathogenesis of the disorder does not per se provide evidence to support the notion that a simple reduction of an NSRE element activity would be reasonably extrapolate to an increase in BDNF that in turns affects HD therapeutically and/or prophylactically. Note also that a reduction of BDNF activity in HD patients is not the same as asserting that an elevated BDNF activity is the magic bullet to treat or prevent BDNF. To add to the complexity of HD pathogenesis, Cattaneo (p. 63, col. 1) reported that HD patients treated with implantation of fetal tissue or injection of BDNF exhibited an interindividual variability in the pathological features of Huntington's

disease lesions. Hence, the patterns of neuronal degeneration are also heterogeneous among patients (p. 62, col. 2). To wit, the authors mention that the number of CAG repeats of the HD gene in families with Huntington's disease, for unknown reasons, increase from generation to generation, and the longer the polyglutamine (e.g. CAG) stretch resulting from the huntingtin mutation, the more toxic the aggregates of mutated huntingtin protein becomes. It appears from the the prior art that even the correlation between the formed aggregates of mutated HD and an neuronal damage observed in Huntington's disease is strongly debated. The issue is whether or not the prior art and the as-filed application provides sufficient guidance and the degrees of predictability as to the structural and functional releationship between the broadly claimed "NSRE" and the treatment and/or prevention of HD. A close review of the entire specification and the prior art does not appear to provide such guidance, particularly in view of the nature and complexity of HD at the molecular level.

Analysis of Quantity of Experimentation

As set forth above by the nature of the invention, neither the prior art of record nor the as-filed specification provides sufficient guidance to enable a person skilled in the art to determine which active materials and/or steps are needed to determine molecules that exhibit an effect in treating or/and preventing Huntington's Disease. How can an broadly claimed evaluation step be performed without an undue experimentation when there is no supporting evidence to substantiate a resonable correlation between an inhibition of NSRE and a HD therapeutic and/or prophylactic effect? Due to the

complexity of HD, an inference regarding a reduction of BDNF activity in HD patients is not sufficient to reasonably conclude that a reduction or complete shut-off of an unspecified NSRE is indicative of the "magic bullet". Even assuming that activity of NRSE is inhibited by a test molecule and thus BDNF transcription is increased, the underlying cause of neuronal death in striatal neurons of Huntington's disease patients and the correlation with increase secretion of NRSE has not been clearly established. As the result, given the unpredictability of the art and the lack of working example in the instant specification, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to practice the instant method to identify and select an enormous number of methods as broadly or generically claimed, with a resultant identification of prevention or treatment of Huntington's disease in a mammalian subject, as claimed.

Conclusion

Claims 1-16 are not allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776 or the examiner's supervisor, Nguyen Dave, can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (571) 273-8300.
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

Maria Leavitt, PhD

Patent Examiner P/1633

Remsen 2B55

Phone: 571-272-1085

Email: maria.leavitt@uspto.gov

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER